

- (203) OLIVER, M.F. Clinical characteristics and prognosis of angina and myocardial infarction in young women. In: Oliver, M.F. (Editor). *Coronary Heart Disease in Young Women*. Edinburgh, Churchill Livingstone, 1978, pp. 221–233.
- (204) ORY, H.W. Association between oral contraceptives and myocardial infarction. A review. *Journal of the American Medical Association* 237(24): 2619–2622, June 13, 1977.
- (205) PAFFENBARGER, R.F., Jr., BRAND, R.J., SHOLTZ, R.I., JUNG, D.L. Energy expenditure, cigarette smoking, and blood pressure level as related to death from specific diseases. *American Journal of Epidemiology* 108(1): 12–18, July 1978.
- (206) PAUL, O., LEPPER, M.H., PHELAN, W.H., DUPERTUIS, G.W., MacMILLAN, A., McKEAN, H., PARK, H. A longitudinal study of coronary heart disease. *Circulation* 28(1): 20–31, July 1963.
- (207) PELKONEN, R., NIKKILA, E.A., KOSKINEN, S., PENTTINEN, K., SARNA, S. Association of serum lipids and obesity with cardiovascular mortality. *British Medical Journal* 2(6096): 1185–1187, November 5, 1977.
- (208) PERPER, J.A., KULLER, L.H., COOPER, M. Arteriosclerosis of coronary arteries in sudden, unexpected deaths. *Circulation* 51 and 52(Supplement III): III-27–III-33, December 1975.
- (209) PETERSSON, B., KRANTZ, P., KRISTENSSON, H., TRELL, E., STERNBY, N.H. Alcohol-related death: A major contributor to mortality in urban middle-aged men. *Lancet* 2(8307): 1088–1090, November 13, 1982.
- (210) PETITTI, D.B., WINGERD, J., PELLEGRIN, F., RAMCHARAN, S. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *Journal of the American Medical Association* 242(11): 1150–1154, September 14, 1979.
- (211) PETO, J. The health effects of smoking in women. In: Ramstrom, I.M. (Editor). *The Smoking Epidemic, a Matter of Worldwide Concern*. Stockholm, Almqvist and Wiksell International, 1979, pp. 45–50.
- (212) PHILLIPS, N.R., HAVEL, R.J., KANE, J.P. Levels and interrelationships of serum and lipoprotein cholesterol and triglycerides. Association with adiposity and the consumption of ethanol, tobacco, and beverages containing caffeine. *Arteriosclerosis* 1(1): 13–24, January/February 1981.
- (213) PHILLIPS, N.R., HAVEL, R.J., KANE, J.P. Serum apolipoprotein A-I levels. Relationship to lipoprotein lipid levels and selected demographic variables. *American Journal of Epidemiology* 116(2): 302–313, August 1982.
- (214) POOLING PROJECT RESEARCH GROUP. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. *Journal of Chronic Diseases* 31(4): 201–306, April 1978.
- (215) RABKIN, S.W., BOYKO, E., STREJA, D.A. Relationship of weight loss and cigarette smoking to changes in high-density lipoprotein cholesterol. *American Journal of Clinical Nutrition* 34(9): 1764–1768, September 1981.
- (216) REGAN, T.J. Alcohol: Is it a risk for cardiovascular disease? *Cardiology Series* 5(4): 6–27, 1982.
- (217) RHOADS, G.G., GULBRANDSEN, C.L., KAGAN, A. Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. *New England Journal of Medicine* 294(6): 293–298, February 5, 1976.
- (218) RICHARD, J.L., DUCIMETIERE, P., BONNAUD, G., CLAUDE, J.R., LELLOUCH, J., SCHWARTZ, D., DiMATTEO, J. Incidence et evaluation du risque de maladie coronarienne: L'etude prospective parisienne. [Incidence and evaluation of risk of coronary heart disease: The Parisian prospective study]. *Archives des Maladies du Cœur et des Vaisseaux* 70(5): 531–540, May 1977.

- (219) RICHTER, B.J., GORI, G.B. Demographic and economic effects of the prevention of early mortality associated with tobacco-related disease. In:Φ: Gori, G.B., Bock, F.G. (Editors). *Banbury Report 3—A Safe Cigarette?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, March 12, 1980, pp. 341–351.
- (220) RISSANEN, V., ROMO, M., SILTANEN, P. Prehospital sudden death from ischaemic heart disease. A postmortem study. *British Heart Journal* 40(9): 1025–1033, September 1978.
- (221) ROBERTSON, T.L., KATO, H., GORDON, T., KAGAN, A., RHOADS, G.G., LAND, C.E., WORTH, R.M., BELSKY, J.L., DOCK, D.S., MIYANISHI, M., KAWAMOTO, S. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Coronary heart disease risk factors in Japan and Hawaii. *American Journal of Cardiology* 39(2): 244–249, February 1977.
- (222) ROBERTSON, T.L., KATO, H., RHOADS, G.G., KAGAN, A., MARMOT, M., SYME, S.L., GORDON, T., WORTH, R.M., BELSKY, J.L., DOCK, D.S., MIYANISHI, M., KAWAMOTO, S. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease. *American Journal of Cardiology* 39(2): 239–243, February 1977.
- (223) ROGOT, E. Cardiorespiratory disease mortality among British and Norwegian migrants to the United States. *American Journal of Epidemiology* 108(3): 181–191, September 1978.
- (224) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213–222, May–June 1980.
- (225) ROSENBERG, H.M., KLEBBA, A.J. Trends in cardiovascular mortality with a focus on ischemic heart disease: United States, 1950–1976. Paper presented at the meeting of the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, October 24–25, 1978. In: Havlik, R.J., Feinleib, M., Thom, T., Kramer, B., Sharrett, A.R., Garrison, R. (Editors). *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, NIH Publication No. 79–1610, May 1979, pp. 11–41.
- (226) ROSENBERG, L., HENNEKENS, C.H., ROSNER, B., BELANGER, C., ROTHMAN, K.J., SPEIZER, F.E. Oral contraceptive use in relation to nonfatal myocardial infarction. *American Journal of Epidemiology* 111(1): 59–66, January 1980.
- (227) ROSENBERG, L., SHAPIRO, S., KAUFMAN, D.W., SLONE, D., MIETTINEN, O.S., STOLLEY, P.D. Cigarette smoking in relation to the risk of myocardial infarction in young women. Modifying influence of age and predisposing factors. *International Journal of Epidemiology* 9(1): 57–63, March 1980.
- (228) ROSENBERG, L., SLONE, D., SHAPIRO, S., KAUFMAN, D., STOLLEY, P.D., MIETTINEN, O.S. Noncontraceptive estrogens and myocardial infarction in young women. *Journal of the American Medical Association* 244(4): 339–342, July 25, 1980.
- (229) ROSENMAN, R.H., BRAND, R.J., JENKINS, C.D., FRIEDMAN, M., STRAUS, R., WURM, M. Coronary heart disease in the Western Collaborative Group study. Final followup experience of 8 1/2 years. *Journal of the American Medical Association* 233(8): 872–877, August 25, 1975.
- (230) ROSS, R. Atherosclerosis: A problem of the biology of arterial wall cells and their interactions with blood components. *Arteriosclerosis* 1(5): 293–311, September/October 1981.

- (231) ROSS, R.K., PAGANINI-HILL, A., MACK, T.M., ARTHUR, M., HENDERSON, B.E. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet* 1(825): 858-860, April 18, 1981.
- (232) ROYAL COLLEGE OF PHYSICIANS. *Smoking Or Health*. A report of the Royal College of Physicians, London, Pitman Medical, 1978, 128 pp.
- (233) SALONEN, J.T. Stopping smoking and long-term mortality after acute myocardial infarction. *British Heart Journal* 43(4): 463-469, April 1980.
- (234) SALONEN, J.T. Oral contraceptives, smoking, and risk of myocardial infarction in young women. A logitudinal population study in eastern Finland. *Acta Medica Scandinavica* 212(3): 141-144, 1982.
- (235) SALONEN, J.T., PUSKA, P. Relation of serum cholesterol and triglycerides to the risk of acute myocardial infarction, cerebral stroke and death in eastern Finnish male population. *International Journal of Epidemiology* 12(1): 26-31, March 1983.
- (236) SAMUELSON, W., WILLIAMS, R.R., MANESS, A.T. Accuracy of death certificates in Utah for myocardial infarction. (Submitted for publication.)
- (237) SCHEIDT, S.S. Angina pectoris: Pathophysiology, precipitating factors, prognosis, and therapy. *Cardiovascular Reviews & Reports* 4(1): 83-90, January 1983.
- (238) SCHLANT, R.C., FORMAN, S., STAMLER, J., CANNER, P.L. The natural history of coronary heart disease: Prognostic factors after recovery from myocardial infarction in 2,789 men. The 5-year findings of the Coronary Drug Project. *Circulation* 66(2): 401-414, August 1982.
- (239) SCHOENENBERGER, J.C. Smoking change in relation to changes in blood pressure, weight, and cholesterol. *Preventive Medicine* 11(4): 441-453, July 1982.
- (240) SCHROLL, M., HAGERUP, L.M. Risk factors of myocardial infarction and death in men aged 50 at entry. A ten-year prospective study from the Glostrup population studies. *Danish Medical Bulletin* 24(6): 252-255, December 1977.
- (241) SEVERI, S., DAVIES, G., MASERI, A., MARZULLO, P., L'ABBATE, A. Long-term prognosis of "variant" angina with medical treatment. *American Journal of Cardiology* 46(1): 226-232, August 1980.
- (242) SHAPIRO, S., ROSENBERG, L., SLONE, D., KAUFMAN, D.W., STOLLEY, P.D., MIETTINEN, O.S. Oral contraceptive use in relation to myocardial infarction. *Lancet* 1(8119): 743-747, April 7, 1979.
- (243) SLONE, D., SHAPIRO, S., KAUFMAN, D.W., ROSENBERG, L., MIETTINEN, O.S., STOLLEY, P.D. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *New England Journal of Medicine* 305(8): 420-424, August 20, 1981.
- (244) SLONE, D., SHAPIRO, S., ROSENBERG, L., KAUFMAN, D.W., HARTZ, S.C., ROSSI, A.C., STOLLEY, P.D., MIETTINEN, O.S. Relation of cigarette smoking to myocardial infarction in young women. *New England Journal of Medicine* 298(23): 1273-1276, June 8, 1978.
- (245) SOLBERG, L.A., STRONG, J.P. Risk factors and atherosclerotic lesions. A review of autopsy studies. *Arteriosclerosis* 3(3): 187-198, May-June 1983.
- (246) SORLIE, P.D., GARCIA-PALMIERI, M.R., COSTAS, R., CRUZ-VIDAL, M., HAVLIK, R. Cigarette smoking and coronary heart disease in Puerto Rico. *Preventive Medicine* 11(3): 304-316, May 1982.
- (247) SPAIN, D.M., BRADESS, V.A., MATERO, A., TARTER, R. Sudden death due to coronary atherosclerotic heart disease. Age, smoking habits, and recent thrombi. *Journal of the American Medical Association* 207(7): 1347-1349, February 17, 1969.

- (248) SPAIN, D.M., BRADESS, V.A., MOHR, C. Coronary atherosclerosis as a cause of unexpected and unexplained death. An autopsy study from 1949-1959. *Journal of the American Medical Association* 174(4): 384-388, September 24, 1961.
- (249) SPAIN, D.M., SIEGEL, H., BRADESS, V.A. Women smokers and sudden death. The relationship of cigarette smoking to coronary disease. *Journal of the American Medical Association* 224(7): 1005-1007, May 14, 1973.
- (250) SPARROW, D., DAWBER, T.R., COLTON, T. The influence of cigarette smoking on prognosis after a first myocardial infarction. A report from the Framingham study. *Journal of Chronic Diseases* 31(6/7): 425-432, 1978.
- (251) STAMLER, J., EPSTEIN, F.H. Coronary heart disease: Risk factors as guides to preventive action. *Preventive Medicine* 1(1-2): 27-48, March 1972.
- (252) STROBEL, M., GSELL, O. Mortalität in Beziehung zum Tabakrauchen. 9 Jahre Beobachtungen bei Ärzten in der Schweiz. [Mortality in relation to tobacco smoking. Nine years of observation in Swiss physicians.] *Helvetica Medica Acta* 32(6): 547-592, December 1965.
- (253) SUGRUE, D.D., THOMPSON, G.R., OAKLEY, C.M., TRAYNER, I.M., STEINER, R.E. Contrasting patterns of coronary atherosclerosis in normocholesterolaemic smokers and patients with familial hypercholesterolaemia. *British Medical Journal* 283(6303): 1358-1360, November 21, 1981.
- (254) TALBOTT, E., KULLER, L.H., DETRE, K., PERPER, J. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. *American Journal of Cardiology* 39(6): 858-864, May 26, 1977.
- (255) TALBOTT, E., KULLER, L.H., PERPER, J., MURPHY, P.A. Sudden unexpected death in women: Biologic and psychosocial origins. *American Journal of Epidemiology* 114(5): 671-682, November 1981.
- (256) THOMAS, P.C., CADY, L.D., O'CONNELL, E.R., BISCHOFF, D.P., KERSHNER, R.K. Heart disease risk factors in Los Angeles County safety personnel. *Journal of Occupational Medicine* 21(10): 683-687, October 1979.
- (257) TOWNSEND, J.L., MEADE, T.W. Ischaemic heart disease mortality risks for smokers and non-smokers. *Journal of Epidemiology and Community Health* 33(4): 243-247, December 1979.
- (258) TYROLER, H.A. Epidemiologic studies of cardiovascular disease in three communities of the southeastern United States. In: Kessler, I.I., Levin, M.L. (Editors). *The Community as an Epidemiologic Laboratory. A Casebook of Community Studies* Baltimore, Johns Hopkins University Press, 1970, pp. 100-122.
- (259) TYROLER, H.A., GLUECK, C.J., CHRISTENSEN, B., KWITEROVICH, P.O., Jr. Plasma high-density lipoprotein cholesterol comparisons in black and white populations. The Lipid Research Clinics Program prevalence study. *Circulation* 62(Supplement IV, part 2): IV-99-IV-107, November 1980.
- (260) UESHIMA, H., IIDA, M., SHIMAMOTO, T., KONISHI, M., TANIGAKI, M., NAKANISHI, N., TAKAYAMA, Y., OZAWA, H., KOJIMA, S., KOMACHI, Y. High-density lipoprotein-cholesterol levels in Japan. *Journal of the American Medical Association* 247(14): 1985-1987, April 9, 1982.
- (261) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking for Women: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980, 359 pp.
- (262) U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: The Changing Cigarette. A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHHS Publication No. (PHS)81-50156, 1981, 252 pp.

- (263) U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. *Smoking and Health: A Report of the Surgeon General*. U.S. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, DHEW Publication No. (PHS)79-50066, 1979, 1136 pp.
- (264) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Report of the Surgeon General: 1971*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Services and Mental Health Administration. DHEW Publication No. (HSM)71-7513, 1971, 458 pp.
- (265) VAN GENT, C.M., VAN DER VOORT, H., HESSEL, L.W. High-density lipoprotein cholesterol, monthly variation and association with cardiovascular risk factors in 1000 forty-year-old Dutch citizens. *Clinica Chimica Acta* 88(1): 155-162, August 15, 1978.
- (266) VAN GENT, C.M., VAN DER VOORT, H., STEGERHOEK, C.J., STYBLO, K. Reduced high-density lipoprotein in women aged 40-41 using oral contraceptives. *Lancet* 1:1221-1223, June 10, 1978.
- (267) VESSEY, M.P., McPHERSON, K., JOHNSON, B. Mortality among women participating in the Oxford/Family Planning Association contraceptive study. *Lancet* 2(8041): 731-733, October 8, 1977.
- (268) VLIETSTRA, R.E., FRYE, R.L., KRONMAL, R.A., SIM, D.A., PHIL, M., TRISTANI, F.E., KILLIP, T. Risk factors and angiographic coronary artery disease: A report from the Coronary Artery Surgery Study (CASS). *Circulation* 62(2): 254-261, August 1980.
- (269) WAHL, P., WALDEN, C., KNOPP, R., HOOVER, J., WALLACE, R., HEISS, G., RIFKIND, B. Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. *New England Journal of Medicine* 308(15): 862-867, April 14, 1983.
- (270) WALD, N.J. Cigarette smoking and coronary heart disease in young women. In: Oliver, M.F. (Editor). *Coronary Heart Disease in Young Women*. Edinburgh, Churchill Livingstone, 1978, pp. 43-58.
- (271) WALD, N., HOWARD, S., SMITH, P.G., KJELDSEN, K. Association between atherosclerotic diseases and carboxyhaemoglobin levels in tobacco smokers. *British Medical Journal* 1(5856): 761-765, March 31, 1973.
- (272) WATERS, D.D., HALPHEN, C., THEROUX, P., DAVID, P.-R., MIZGALA, H.F. Coronary artery disease in young women: Clinical and angiographic features and correlation with risk factors. *American Journal of Cardiology* 42(1): 41-47, July 1978.
- (273) WEAVER, W.D., LORCH, G.S., ALVAREZ, H.A., COBB, L.A. Angiographic findings and prognostic indicators in patients resuscitated from sudden cardiac death. *Circulation* 54(6): 895-900, December 1976.
- (274) WEIR, J.M., DUNN, J.E., Jr. Smoking and mortality: A prospective study. *Cancer* 25(1): 105-112, January 1970.
- (275) WERKO, L. Can we prevent heart disease? *Annals of Internal Medicine* 74(2): 278-288, February 1971.
- (276) WHITE, P.D. Coronary disease and coronary thrombosis in youth. An analysis of 4 cases under the age of thirty years, 21 cases under the age of forty years, and 138 cases under the age of fifty years. *Journal of the Medical Society of New Jersey* 32(10): 596-605, October 1935.
- (277) WHYTE, H.M. The relative importance of the major risk factors in atherosclerotic and other diseases. *Australian and New Zealand Journal of Medicine* 6: 387-393, 1976.

- (278) WILHELMSSEN, L. Risk factors for disease according to population studies in Göteborg, Sweden. Paper presented at Skandia International Symposia, September 23-25, 1980. In: Bostrom, H., Ljungstedt, N. (Editors). *Medical Aspects of Mortality Statistics*. Skandia International Symposia. Stockholm, Almquist and Wiksell International, 1981, pp. 73-88.
- (279) WILHELMSSEN, L., BENGTSSON, C., ELMFELDT, D., VEDIN, A., WILHELMSSON, C., TIBBLIN, G., LINDQVIST, O., WEDEL, H. Multiple risk prediction of myocardial infarction in women as compared with men. *British Heart Journal* 39(11): 1179-1185, November 1977.
- (280) WILLETT, W.C., HENNEKENS, C.H., BAIN, C., ROSNER, B., SPEIZER, F.E. Cigarette smoking and non-fatal myocardial infarction in women. *American Journal of Epidemiology* 113(5): 575-582, May 1981.
- (281) WILLETT, W., HENNEKENS, C.H., CASTELLI, W., ROSNER, B., EVANS, D., TAYLOR, J., KASS, E.H. Effects of cigarette smoking on fasting triglyceride, total cholesterol, and HDL-cholesterol in women. *American Heart Journal* 105(3): 417-421, March 1983.
- (282) WILLETT, W., STAMPFER, M.J., BAIN, C., LIPNICK, R., SPEIZER, F.E., ROSNER, B., CRAMER, D., HENNEKENS, C.H. Cigarette smoking, relative weight, and menopause. *American Journal of Epidemiology* 117(6): 651-658, June 1983.
- (283) WINKELSTEIN, W., Jr., REKATE, A.C. Age trend of mortality from coronary artery disease in women and observations on the reproductive patterns of those affected. *American Heart Journal* 67(4): 481-488, April 1968.
- (284) WORTH, R.M., KATO, H., RHOADS, G.G., KAGAN, A., SYME, S.L. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: Mortality. *American Journal of Epidemiology* 102(6): 481-480, December 1975.
- (285) WYNDER, E.L., LEMON, F.R. Cancer, coronary artery disease and smoking. A preliminary report on differences in incidence between Seventh-Day Adventists and others. *California Medicine* 89(4): 267-272, October 1958.

## **SECTION 4. CEREBROVASCULAR DISEASE**

## **Introduction**

Death rates from stroke have been declining in developed countries since the 1920s (28). Between 1968 and 1975 there was a sharp decline in the age-adjusted mortality rates from coronary heart disease, cerebrovascular diseases, and all major cardiovascular diseases among U.S. white and nonwhite males and females (50). As shown in Table 1, the decrease is close to 33 percent for stroke.

Additional major reductions in disability and death from stroke can come largely from preventive measures, not from further innovations in treatment of the completed catastrophe. Formulation of a preventive program is greatly aided by an understanding of the epidemiology of cerebrovascular disease, including the chain of circumstances leading to its occurrence, the identity of vulnerable subgroups of the population, the existence of modifiable predisposing factors, and the natural history of the disease.

## **Magnitude of the Problem**

Cerebrovascular diseases, both ischemic and hemorrhagic, are a public health problem of major proportions. They constitute the third leading cause of death, after coronary heart disease and cancer, and are responsible for 9 percent of all deaths in the United States (33). There are about 1.8 million stroke victims in the United States, and about a half-million new events occur each year; there are approximately 200,000 deaths annually in the United States from strokes. In the Framingham study it was estimated that the chances of suffering a stroke before age 70 are 1 in 20. The incidence was found to double in each successive decade after age 45. Although stroke incidence becomes substantial only after age 65, 20 percent of strokes occur before that age. In men, the average annual incidence of atherothrombotic brain infarction is only one-third that of myocardial infarction, with stroke incidence lagging behind myocardial infarction by more than 10 years. In women, on the other hand, brain infarction incidence and myocardial infarction incidence are virtually identical (56). The reasons that brain infarction is manifested later in life than CHD in men and exhibits little male predominance are unclear. In the United States, stroke mortality is higher among blacks than among whites, and the difference decreases with age.

## **The Stroke Entity**

There are three major specific forms of cerebrovascular diseases: (1) cerebral insufficiency associated with transient blood flow deficiencies; (2) cerebral infarction caused either by the blocking of a vessel by an embolism or by thrombosis; and (3) cerebral hemorrhage, including parenchymal and subarachnoid. The terms "stroke"

**TABLE 1.—Percentage of change in mortality rates of causes of death in persons aged 35 to 74, by sex and color, United States, 1968–1976**

Cause of death	Percentage of change				All
	White men	White women	Nonwhite men	Nonwhite women	
Coronary heart disease	-21.0	-26.5	-30.7	-39.1	-24.3
Cerebrovascular diseases	-30.6	-30.4	-43.7	-47.1	-32.7
Major cardiovascular diseases	-20.9	-26.1	-33.2	-40.7	-24.6
All causes	-15.3	-16.4	-24.8	-32.7	-17.3

SOURCE: Stamler (50).

and "cerebral vascular accident" are nonspecific; they refer to a variety of clinical entities and are usually used in reference to syndromes accompanying ischemic or hemorrhagic lesions.

The underlying process of a stroke may be an atheroma (i.e., fatty deposit in the inner lining of an artery wall), thrombosis, embolism, a bleeding disorder, a developmental anomaly, an aneurysm, inflammation, failure of flow, or increased blood viscosity. The chief causes of cerebral ischemia are atherothrombosis and embolism. Intracranial hemorrhage is generally due to hypertensive intracerebral hemorrhage, rupture of a saccular aneurysm, or bleeding from an arteriovenous malformation. A cerebral embolism usually originates in the heart, particularly when atrial fibrillation, rheumatic valvular deformity, myocardial infarction with a mural thrombus, or a valve prosthesis is present; it may also arise from ulcerated atheroma in the carotid, vertebrobasilar, or middle cerebral arteries. The main trunk of the middle cerebral artery and its branches are the most common sites for the formation of intracranial thrombosis.

The reliability of stroke diagnoses and case ascertainment in diverse populations has presented problems for epidemiological and clinical research. With the fairly recent development of new technology such as computer-assisted tomography, however, the accuracy and the quality of differential diagnosis as to type of stroke are improving. It is unlikely that any single etiology or set of risk factors applies equally to all types of stroke. Atherothrombotic brain infarction is the most common variety of stroke, accounting for about 59 percent of the total number of strokes in the Framingham population (56).

### Cardiovascular Risk Factors

Since the underlying pathologic features of atherosclerosis in the cerebral, cardiac, and peripheral circulation are virtually identical,

it is not unexpected to find that they share a number of precursors. Although some significant differences in their impact exist, there are a number of modifiable risk factors common to brain and myocardial infarction (22). In fact, when five major cardiovascular risk factors (systolic blood pressure, serum cholesterol, glucose intolerance, cigarette smoking, and electrocardiogram-left ventricular hypertrophy (ECG-LVH)) are considered jointly as a cardiovascular risk profile, they are actually more highly predictive of brain infarction than of coronary heart disease (24). The top decile of multivariate risk using this profile identifies half the strokes evolving in the Framingham population, compared with only 25 percent of the coronary events (22). However, for cerebrovascular disease, systolic blood pressure and ECG-LVH were the chief determinants of this multivariate predictive capacity. In addition to these risk predictors, various cardiac impairments such as coronary heart disease, cardiac failure, and atrial fibrillation are major predisposing factors (55). Cigarette smoking, which is a major predictor for coronary heart disease, has been less consistently predictive for cerebrovascular disease; but nevertheless appears to play a significant role among men at younger ages.

### **Hypertension**

A consistent finding in epidemiologic studies is that elevated blood pressure is the most important risk factor for stroke. This seems to apply for virtually all varieties of stroke (56). It is the key risk factor for intracerebral hemorrhage, occlusive cerebral vascular disease, and perhaps subarachnoid hemorrhage (28). About 50 to 60 percent of strokes occur in the 20 percent of the population with definite hypertension. Hypertension predisposes powerfully to stroke at all ages and in both sexes, and even mild elevations in blood pressure double the risk. The stroke risk for isolated systolic hypertension is substantial, and the exclusive use of diastolic pressure to judge the risk in the elderly with systolic hypertension can be misleading. No component of blood pressure, including the pulse pressure, mean arterial pressure, or diastolic pressure, is more closely related to stroke incidence than systolic pressure (25). Also, lability of the pressure has not been shown to reduce the risk, and it is not safe to use the lowest pressure recorded to determine whether treatment is indicated.

### **Blood Lipids**

Lipids and their lipoprotein vehicles, closely linked to coronary disease incidence, are of uncertain importance for stroke. Neither cholesterol nor triglyceride levels have any predictive value beyond age 55, when strokes are common, and partition of the serum total cholesterol into its atherogenic low density lipoprotein (LDL) and

protective high density lipoprotein (HDL) components does not clarify the role of cholesterol in stroke as it does for coronary heart disease in advanced age (11). In women there is actually a paradoxical, strong negative association of brain infarction incidence with LDL cholesterol. This inverse relationship to atherogenic cholesterol has also been noted in Japanese men and for intracerebral hemorrhage (19). Hence, further clarification is needed.

### **Glucose**

Atherothrombotic brain infarction incidence is increased threefold in diabetics. In contrast to coronary heart disease, the impact of impaired glucose tolerance does not diminish with advancing age and is not greater for women than for men. The effect of diabetes mellitus is independent of other risk factors, but is greatly influenced by coexistent hypertension or cardiac disease (23).

### **Cardiac Disease**

Even if asymptomatic, cardiac changes such as ECG-LVH, cardiac enlargement on X-ray, atrial fibrillation, coronary disease, cardiac failure, or rheumatic heart disease powerfully predispose to the occurrence of strokes. ECG-LVH is the most powerful ECG predictor. Atrial fibrillation, chronic as well as intermittent, increases stroke risk sixfold, and when accompanied by rheumatic heart disease, seventeenfold (55). Although each contributes independently to risk, coexistent hypertension further augments the risk associated with any cardiac impairment.

### **Environmental Factors**

Few modifiable environmental contributors to stroke incidence have been convincingly demonstrated. The demonstrated association of obesity with stroke incidence appears to derive mainly from the higher blood pressure and glucose intolerance that it promotes. Physical activity is weakly and inconsistently related to stroke incidence (55). The apparent influence of coffee intake disappears on adjustment for coexistent alcohol and cigarette use. Alcohol seems to be associated with an increased risk of stroke in some studies, possibly because of higher blood pressure in alcohol users.

### **Cigarette Smoking**

The contribution of cigarette smoking to the incidence of stroke may vary depending on the type of stroke or clinical manifestation of cerebrovascular disease. The evidence for such a relationship suggests that smoking is more strongly associated with premature (i.e., before age 55) and nonfatal strokes than with fatal strokes (22).

With 16 years of followup data on 293,000 insured U.S. veterans, Rogot and Murray (43) reported that 653 excess stroke deaths were associated with cigarette smoking, producing a mortality ratio of 1.47. Earlier, with 8.5 years of followup, Kahn (21) had found stroke mortality to be 1.4 times higher in smokers and rates to increase with amount smoked. In the more recent study, a slight dose-response relationship was found for both current and ex-smokers, with mortality ratios lower among former smokers than among current smokers. Mortality ratios for stroke were near unity for smokers of only cigars or pipes—1.07 and 0.99, respectively (43). A study of 54,460 men employed in British industries revealed no relationship between the cigarette habit and stroke mortality over 3 years, but demonstrated a threefold excess coronary mortality (3).

Kuller (28), in a review of the epidemiology of stroke, concluded that there was no consistent evidence of a relationship of cigarette smoking to stroke in several population and case-control studies. Data after 24 years of followup in the Framingham study showed no overall statistically significant relationship between the incidence of atherothrombotic brain infarction (ABI) and cigarette smoking among males. The stroke incidence was lower in nonsmoking males only between the ages of 45 and 54, and no clear dose-response was evident (56). In a comparison of stroke prevalence—not specified as to type—among Japanese in Japan, Hawaii, and California, preliminary analyses revealed positive correlations between stroke and increased blood pressure, ECG-LVH, and cigarette smoking for all ages (20). Paffenbarger et al. (37) found no relationship between cigarette smoking and stroke in a 22-year followup of 3,686 long-shoremen.

In an earlier study of chronic diseases among male former students at Harvard, Paffenbarger and Wing (38) noted a slight excess of nonfatal stroke among those who had smoked during college. They also found that hypertension, overweight, and short stature were predisposing characteristics for stroke in later life. The data must be interpreted with some caution, however, because they were abstracted from existing school records and the smoking information was not collected in a standardized manner. In a Canadian retrospective study (1), a relative risk of 2.4 ( $p < 0.001$ ) was found for stroke and smoking, but these results are also subject to potential bias in the recording of the smoking history.

Hammond and Horn (15) studied the relationship between smoking and disease among 187,783 white men, 50 to 69 years old, followed from May 1952 through October 1955. Of the 11,870 deaths during this period, 1,050 were from cerebral vascular lesions. A statistically significant mortality ratio of 1.30 was found for smokers and a dose-response relationship was apparent.

**TABLE 2.—Mortality ratios for cerebrovascular disease related to smoking, United States, 1969<sup>1</sup>**

Cigarettes/day	Mortality ratios ( <i>N</i> =4,099), by age			
	40-49	50-59	60-69	70-79
<b>Males</b>				
Never smoked	1.00	1.00	1.00	1.00
1-9	2.79	1.95	1.30	0.95
10-19	1.14	1.48	1.44 <sup>2</sup>	0.92
20-30	2.21	2.03	1.62	1.22
>40	1.64	2.40	1.72	0.68 <sup>2</sup>
<b>Females</b>				
Never smoked	1.00	1.00	1.00	1.00
1-9	1.50	1.26	1.26	0.83
10-19	2.60	2.70	2.15	0.57 <sup>2</sup>
20-30	2.90	2.67	1.83	1.28
>40	5.70 <sup>2</sup>	3.52 <sup>2</sup>	—	—

<sup>1</sup> Population included 358,584 males and 445,875 females, 40-79 years of age at entry. Data collected from questionnaire and 6-year followup of death certificate.

<sup>2</sup> Based on only five to nine deaths.

SOURCE: Hammond and Garfinkel (14).

In a large-scale prospective study of male British physicians, Doll and Hill (8) found that the results differed somewhat between the 10th and 20th year of followup. A stroke mortality ratio of 1.2 was found for smokers at the 10-year followup, with no dose-response relationship evident. After 20 years of followup, a relative risk for cerebral thrombosis of 1.52 was found for heavy smokers and a strong dose-response relationship was apparent (9).

In an analysis of the 1,094 deaths that occurred among female British physicians who had been followed for 22 years, Doll et al. (7) found no effect of smoking on mortality from cerebral thrombosis; however, there were only 68 such deaths.

The American Cancer Society studied prospectively more than a million men and women enrolled in 1959, following them for 13 years. With 6 years of followup, mortality ratios for cerebral vascular disease were found to be increased among male and female smokers compared with nonsmokers, with the highest ratios evident among the 40- to 49-year-olds (Table 2). The excess risk was not present in either sex past age 70. There was no significant dose-response relationship (13, 14).

A study of the differences in mortality ratios by the type of cigarette smoked (29) and a later analysis of data from the American Cancer Society study indicated lower mortality ratios from stroke among males who smoked low tar and nicotine or filtered cigarettes than among smokers of higher tar and nicotine cigarettes or of "plain" cigarettes (6). No such differences were found among

females. A study conducted by the Tobacco Research Council in England showed mortality ratios that were lower, but not significantly so, among smokers of lower tar and nicotine cigarettes (6).

In 1965, Ostfeld began a prospective study among random samples of the elderly in Cook County, Illinois, to determine variables associated with stroke. They found that stroke-prone persons can be identified even among the elderly. Stroke risk was higher among the blacks and among persons with preexisting cardiovascular disease, transient ischemic attacks (TIAs), diabetes mellitus, or hypertensive cardiovascular disease. Cigarette smoking was, however, unrelated to any class of stroke in the elderly, with or without preexisting cardiovascular precursors (36).

Kimura (26) reviewed the results of six prospective studies of cardiovascular disease in Japan and found a correlation of cigarette smoking with myocardial infarction when accompanied by abnormalities in serum cholesterol and blood pressure; no relationship of cigarette smoking to stroke was noted. Okada et al. (34) studied stroke prospectively in Japanese men 40 years old or older residing in two rural communities and found relative risks of intracerebral hemorrhage and brain infarction among nonsmokers that were not statistically significantly lower than those in smokers.

In an 8-year prospective study of a random sample of 35- to 59-year-olds in two counties in eastern Finland, age, blood pressure, diabetes mellitus, and previous stroke were found to be predictive of stroke incidence in both men and women. Cigarette smoking and serum triglyceride levels were found to be positively associated with stroke among men, but not among the women (47). In an effort to predict coronary heart disease and other mortality rates, Menotti et al. (32) analyzed 14 CHD risk factors using a multiple logistic function model. The study included 1,524 men between 40 and 59 from two rural areas in Italy who were measured for all 14 risk factors upon entry. After 15 years, 37 men had had a stroke. Of the 14 risk factors considered, age and blood pressure were the only factors found to be significantly associated with stroke risk, ranking 1 and 2, respectively. Smoking ranked third for predicting stroke, but was not statistically significant.

In a retrospective study (16) of 126 stroke patients and 212 matched controls in Tilburg, Holland, a significantly increased risk of stroke associated with cigarette smoking was not found. Hypertension was found to be related to stroke, and the risk was age dependent, being strongest among the younger patients.

An investigation in Finland (10) of 128 men and 85 women under 50 years of age with ischemic stroke revealed 1.5 times as many cigarette-smoking men and three times as many cigarette-smoking women in the stroke group as in the Finnish population of the same age. Hypertension, abnormal electrocardiographic findings, and oral

contraceptive use in women were also shown to increase risk. In a large prospective study (40) of women under 55 years of age in California who were followed for 6.5 years, cigarette smoking increased the risk of subarachnoid hemorrhage 5.7 times and use of oral contraceptives increased it 6.5 times. The relative risk was 21.9 among women who both smoked and used the pill compared with nonsmoking nonusers. In a case-control study (4) involving 12 university hospitals, 598 nonpregnant women with strokes between age 15 and 44 were identified. Compared with controls, current use of oral contraceptives was considerably higher in women with thrombotic strokes (ninefold) and somewhat higher in women with hemorrhagic strokes. It was also found that 74 percent were current or past smokers. In an investigation of 75 hemiplegics aged 18 to 50 years, Steinmann (51) found that cardiac disease and hypertension were the predominant risk factors. In men, but not in women, heavy smoking was a risk factor.

Further confirming the general impression that cigarette smoking is a stroke risk factor in young men are the results of three case-control studies. Among 100 male stroke patients, aged 40 to 69, Koch et al. (27) found a relative risk of 11.2 for smokers of more than 20 cigarettes a day. In a study (30) of 56 male and 34 female patients under 66 years of age with cerebral hemorrhage or infarction, significantly more stroke patients than their matched controls were found to be smokers, and more smoked at least a pack of cigarettes a day. Other factors predisposing to stroke in this study population were high blood pressure, oral contraceptive use, and a family history of stroke, plus cerebral neoplasm and thrombocytopenia. In another study (52), among 39 male and 28 female ischemic stroke patients, cigarette smoking was found significantly more frequently among male cases than among matched controls. In the young females, use of oral contraceptives was the predominant risk factor.

Haberman et al. (12) summarized mortality and incidence studies dealing with smoking and stroke (Tables 3 and 4). They pointed out that the relationship between smoking and cerebrovascular disease is not a uniform finding of the epidemiologic studies of this disease process. The authors cautioned that the studies are not strictly comparable because of variations in methodologies, but they suggested that an association between smoking and stroke may exist but be age dependent. An age dependency is suggested by the Framingham and Paffenbarger studies.

### **Transient Ischemic Attacks**

Some evidence connects cigarette smoking with transient ischemic attacks (TIA). In a 6-year followup for TIA of 7,895 men aged 45 to 68 years in the Honolulu heart study (41), prior cigarette smoking was

**TABLE 3.—Results of stroke incidence studies**

Study	Type <sup>1</sup>	Date	Disease <sup>2</sup>	Relationship between stroke and smoking <sup>3</sup>	Approximate relative risk
Hiroshima	P	1958-64	CI	None	-
Washington	P	1961-71	Stroke	None	0.9
			CI	None	0.8-1.1
Framingham	P	1949-73	ABI	Yes. Not sig	1.1-2.7 (males)
Manitoba	R	1970-71	CI	Yes. Sig?	2.4
Rural Japan	P	1964-70	Stroke	Yes. Not sig	1.9-2.7
Harvard	P	1916-66	Nonfatal CI	Yes. Sig	1.6
Walnut Creek	P	1969-76	SAH	Yes. Sig	5.7
Queen Square	R	1965-78	Aneurysm	Yes. Sig?	3.8

<sup>1</sup> P denotes prospective; R denotes retrospective.

<sup>2</sup> CI: cerebral infarction; ABI: atherothrombotic brain infarction; SAH: subarachnoid hemorrhage.

<sup>3</sup> ? denotes doubt about the study design.

SOURCE: Haberman et al. (12).

**TABLE 4.—Results of stroke mortality studies**

Name	Type <sup>1</sup>	Date	Relationship between stroke and smoking	Approximate mortality ratio
Longshoremen	P	1951-69	None	1.1
Washington	P, R	1962-71	None	0.9
Harvard	P	1916-66	Yes	2.1
Dorn	P	1954-62	Yes	1.3-1.9
British doctors (10 year)	P	1951-61	None	1.2
British doctors (20 year)	P*	1951-71	Yes	1.1-1.5
American Cancer Society	P	1959-65	Yes	1.3-2.8

<sup>1</sup> P denotes prospective; R denotes retrospective.

\* Based on cerebral thrombosis only.

SOURCE: Haberman et al. (12).

associated with TIA, even in multivariate analysis taking other risks into account. However, Ostfeld et al. (35) found conflicting results.

### Subarachnoid Hemorrhage

A retrospective study (2) of patients with subarachnoid hemorrhage demonstrated an association with cigarette smoking. In this study, smoking was estimated to increase the risk of a subarachnoid hemorrhage almost fourfold in both sexes. In the Walnut Creek contraceptive study this was confirmed, with a 5.7-fold increased risk compared with nonsmokers (39). Also, in a 6.5-year followup of this cohort of 16,759 white middle-class women aged 18 to 54, cigarette smoking was associated with a fivefold to sevenfold relative risk of subarachnoid hemorrhage and also with a 4.8-fold risk for other strokes (40).

### Smoking Cessation

Controlled clinical trial data measuring the effect of smoking cessation on cerebrovascular disease are not available; observational studies have been published. In the 16-year followup of 293,000 insured veterans (43), specific causes of death were studied in relation to smoking status. Mortality ratios for ex-smokers were found to be much lower than for current smokers. For stroke, the mortality risk for the ex-smoker rapidly returned to the nonsmoker rate after the cessation of smoking. Koch et al. (27) found an increased risk of stroke in young patients that was not detectable in ex-smokers after 1 year.

### Oral Contraceptives

Oral contraceptives (OCs) have been widely used for more than 20 years, and many reports suggest that women who use them are at increased risk of stroke (4, 5, 18, 44, 53, 54). Firm, undistorted prospective data on the risk of cigarette smoking in women taking OCs are sparse, owing to the generally low incidence of stroke in women of childbearing age. Reliance is placed chiefly on retrospective data subject to unavoidable selective bias or on multicenter prospective data based on small numbers of events. Such data as exist strongly suggest a synergistic effect of smoking and oral contraceptives that may be related to "hemorrhagic stroke" (42, 46).

In 1969, the Walnut Creek Contraceptive Drug Study began a long-term study of the effects of OC use on the health of women aged 18 to 54 at study initiation. After 6.5 years of followup, Petitti and Wingerd (39) analyzed the data from 15,260 women. The authors found relative risks associated with OC use of 6.5 and 7.6 for subarachnoid hemorrhage and thromboembolism, respectively. The risk of subarachnoid hemorrhage for smokers was 5.7 times that for nonsmokers; the relative risk of subarachnoid hemorrhage for women who smoked and used oral contraceptives was 21.9. Among the small number of ex-users, past use significantly increased the risk of subarachnoid hemorrhage, but not of other vascular diseases (39). In another study, cigarette smoking in itself was evidently not a demonstrable risk factor for stroke among women, even at an early age (42).

In a two-part review article, Stadel (48, 49) indicates that OC use multiplies, rather than adds to, the risk of age and other factors in the development of myocardial infarction (MI) and stroke. On the basis of a total of only 31 cases reported in two studies and 134 reported in a third, Stadel (49) further indicates that current and past use of OCs appears to increase the risk of subarachnoid hemorrhage in women near age 35 or older (17). Stadel suggests that the risk of cardiovascular disease among current users of oral

**TABLE 5.—Annual death rate for oral contraceptive users related to age, duration of use, and smoking habits**

User characteristic	Annual death rate
Age group	
15-34 years	1 per 20,000
35-44 years	1 per 3,000
45-49 years	1 per 700
Duration of use	
< 5 years	1 per 8,000
> 5 years	1 per 2,000
Smoking habit	
Nonsmoker	1 per 10,000
Smoker	1 per 3,000

SOURCE: McQueen (37); Royal College of General Practitioners (44).

contraceptives is related to the estrogen and progestogen content of the pill.

A large prospective study in England (46,000 British women) found that both the incidence and the mortality rates of a variety of diseases, including cerebrovascular disease, were increased among users of oral contraceptives versus nonusers (45). The number of stroke deaths in the Royal College of General Practitioners (RCGP) study was small; thus, risk estimates were subject to error. Women over 35 and women who smoked and took oral contraceptives were found to be at substantially higher risk than were nonsmokers and nonusers of OCs.

Additional analysis of the RCGP study including followup through 1976 showed that current or previous users of oral contraceptives had a standardized mortality rate for cerebrovascular disease 4.7 times that of controls. Increases in total death rates were found among older women, women who had used the pill for 5 or more years, and women who smoked cigarettes (44) (Table 5).

Results from a case-control study conducted by the Collaborative Group for the Study of Stroke in Young Women (5) showed that cigarette smoking and the use of oral contraceptives were independent risk factors for subarachnoid hemorrhage; the relative risk was 2.6 for smokers and 4.1 for users of OCs. When a heavy smoker also took oral contraceptives, the risk increased to 6.1 or 7.6, depending upon the control group used for comparison. In an earlier report, the same group (4) reported that risk of cerebral ischemia or thrombosis was approximately nine times greater among women using oral contraceptives than among nonusing controls. They also reported

lower incidence rates among black women than among white women and that more of the cases than of the controls were or had been regular smokers.

The data suggest that cigarette smokers who use oral contraception are at significantly increased risk of stroke and that this risk may result from a synergistic interaction between cigarette smoking and the use of oral contraceptives.

### **Preventive Implications**

Declining trends in stroke mortality and the marked geographic variation suggest that cerebrovascular disease may not be an inevitable consequence of aging or of genetic makeup. High risk candidates can be identified using a general cardiovascular risk profile. There is as yet no conclusive evidence that intervening to lower lipids, reduce overweight, provide exercise, treat diabetes mellitus, or stop cigarette smoking will in fact reduce stroke risk. However, former cigarette smokers appear to have a lower risk of stroke than do continuing smokers.

The key to stroke prevention is early, vigorous, sustained control of hypertension and the cardiac impairments that escalate the risk. Cigarette smoking cessation may also play a role, particularly in young male stroke candidates or in women using oral contraceptives.

### **Summary**

A preventive approach to stroke is imperative because central nervous system damage often leads to an irreversible functional deficit. Less than a third of stroke victims have symptoms warning of the impending stroke. The similarity of factors predisposing to stroke and those increasing susceptibility to coronary heart disease and congestive heart failure indicates that vascular disease of the brain is part of a larger problem of cardiovascular disease. The measures indicated for prevention of stroke include those recommended for prevention of coronary heart disease, occlusive peripheral arterial disease, and congestive heart failure. Hypertension is clearly the major contributor to stroke incidence. Cigarette smoking also contributes, especially in younger populations, and may be important because of its demonstrated relationship to coronary heart disease and congestive heart failure, which powerfully contribute to stroke risk. Cigarette smoking cessation is indicated as part of a comprehensive program of risk factor modification to avoid atherosclerotic cardiovascular disease, including stroke.

Women cigarette smokers experience an increased risk for subarachnoid hemorrhage; the use of both cigarettes and oral contraceptives appears to synergistically increase this risk.

## **Conclusions**

1. Data from numerous prospective mortality studies have shown an association between cigarette smoking and cerebrovascular disease. This risk is most evident in the younger age groups, and the effect diminishes with increasing age, with little or no effect noted after age 65. No consistent dose-response effect has been demonstrated.
2. Women cigarette smokers experience an increased risk for subarachnoid hemorrhage. However, the use of both cigarettes and oral contraceptives greatly increases the risk for subarachnoid hemorrhage among women.

## References

- (1) ABU-ZEID, H.A.H., CHOI, N.W., MAINI, K.K., HSU, P.-H., NELSON, N.A. Relative role of factors associated with cerebral infarction and cerebral hemorrhage. *Stroke* 8(1): 106-112, January-February 1977.
- (2) BELL, B.A., SYMON, L. Smoking and subarachnoid haemorrhage. *British Medical Journal* 1(6163): 577-582, March 3, 1979.
- (3) BRETT, G.Z., BENJAMIN, B. Smoking habits of men employed in industry, and mortality. *British Medical Journal* 3(5610): 82-85, July 13, 1968.
- (4) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraception and increased risk of cerebral ischemia or thrombosis. *New England Journal of Medicine* 288(17): 871-878, April 26, 1973.
- (5) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraceptives and stroke in young women. Associated risk factors. *Journal of the American Medical Association* 231(7): 718-722, February 17, 1975.
- (6) DEAN, G., LEE, P.N., TODD, G.F., WICKEN, A.J. *Report on a Second Retrospective Mortality Study in North-East England. Part I: Factors related to mortality from lung cancer, bronchitis, heart disease and stroke in Cleveland County, with a particular emphasis on the relative risks associated with smoking filter and plain cigarettes.* Tobacco Research Council, Research Paper 14, London, 1977, 95 pp.
- (7) DOLL, R., GRAY, R., HAFNER, B., PETO, R. Mortality in relation to smoking: 22 years' observations on female British doctors. *British Medical Journal* 280(6219): 967-971, April 5, 1980.
- (8) DOLL, R., HILL, A.B. Mortality in relation to smoking: Ten years' observations of British doctors. *British Medical Journal* 1(5395): 1399-1410, May 30, 1964.
- (9) DOLL, R., PETO, R. Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal* 2(6051): 1525-1536, December 25, 1976.
- (10) FOGELHOLM, R., AHO, K. Ischaemic cerebrovascular disease in young adults. I. Smoking habits, use of oral contraceptives, relative weight, blood pressure and electrocardiographic findings. *Acta Neurologica Scandinavica* 49(4): 415-427, 1973.
- (11) GORDON, T., KANNEL, W.B., CASTELLI, W.P., DAWBER, T.R. Lipoproteins, cardiovascular disease, and death. The Framingham study. *Archives of Internal Medicine* 141(9): 1128-1131, August 1981.
- (12) HABERMAN, S., CAPILDEO, R., ROSE, F.C. Smoking: A risk factor for stroke? In: Greenhalgh, R.M. (Editor). *Smoking and Arterial Disease*. Bath, Great Britain, Pitman Press, 1981, pp. 17-28.
- (13) HAMMOND, E.C. Smoking in relation to the death rates of one million men and women. In: Haenszel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph No. 19, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 127-204.
- (14) HAMMOND, E.C., GARFINKEL, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* 19(2): 167-182, August 1969.
- (15) HAMMOND, E.C., HORN, D. Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. I. Total mortality. *Journal of the American Medical Association* 166(10): 1159-1172, March 8, 1958.

- (16) HERMAN, B., LEYTEN, A.C.M., Van LUIJK, J.H., FRENKEN, C.W.G.M., OPDECOUL, A.A.W., SCHULTE, B.P.M. An evaluation of risk factors for stroke in a Dutch community. *Stroke* 13(3): 334-339, May-June, 1982.
- (17) INMAN, W.H.W. Oral contraceptives and fatal subarachnoid hemorrhage. *British Medical Journal* 2(6202): 1468-1470, December 1, 1979.
- (18) JICK, H., PORTER, J., ROTHMAN, K.J. Oral contraceptives and nonfatal stroke in healthy young women. *Annals of Internal Medicine* 89(1): 58-60, July 1978.
- (19) KAGAN, A., POPPER, J.S., RHOADS, G.G. Factors related to stroke incidence in Hawaii Japanese men: The Honolulu heart study. *Stroke* 11(1): 14-21, January-February 1980.
- (20) KAGAN, A., POPPER, J.S., RHOADS, G.G., TAKEYA, Y., KATO, H., GOODE, G.B., MARMOT, M. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: Prevalence of stroke. In: Scheinberg, P. (Editor). *Cerebrovascular Diseases*. New York, Raven Press, 1976, pp. 267-277.
- (21) KAHN, H.A. The Dorn study of smoking and mortality among U.S. veterans: Report on 8 and one-half years of observation. In: Haenzel, W. (Editor). *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. National Cancer Institute Monograph No. 19, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, January 1966, pp. 1-125.
- (22) KANNEL, W.B. Epidemiologic studies on smoking in cerebral and peripheral vascular disease. In: Wynder, E.L., Hoffmann, D., Gori, G.B. (Editors). *Modifying the Risk for the Smoker*. Volume 1. Proceedings of the Third World Congress on Smoking and Health, New York, June 2-5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)76-1221, 1976, pp. 257-274.
- (23) KANNEL, W.B., McGEE, D.L. Diabetes and cardiovascular disease. The Framingham study. *Journal of the American Medical Association* 241(19): 2035-2038, May 11, 1979.
- (24) KANNEL, W.B., McGEE, D.L., GORDON, T. A general cardiovascular risk profile: The Framingham study. *American Journal of Cardiology* 38(1): 46-51, July 1976.
- (25) KANNEL, W.B., WOLF, P.A., McGEE, D.L., DAWBER, T.R., McNAMARA, P., CASTELLI, W.P. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham study. *Journal of the American Medical Association* 245(12): 1225-1229, March 27, 1981.
- (26) KIMURA, N. Epidemiological studies in Japan on smoking and cardiovascular disease. In: Steinfeld, J., Griffiths, W., Ball, K., Taylor, R.M. (Editors). *Health Consequences, Education, Cessation Activities and Governmental Action*. Volume II. Proceedings of the Third World Conference on Smoking and Health, New York, June 2-5, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, DHEW Publication No. (NIH)77-1413, 1977, pp. 185-192.
- (27) KOCH, A., REUTHER, R., BOOS, R., REUTHER, E., MOERL, H. Risikofaktoren bei cerebralen Durchblutungsstörungen. [Risk factors of cerebral blood circulation disorders.] *Verhandlungen der Deutschen Gesellschaft für Innere Medizin* 83: 1773-1776, 1977.
- (28) KULLER, L.H. Epidemiology of stroke. In: Schoenberg, D.S. (Editor). *Neurological Epidemiology: Principles and Clinical Applications*. Advances in Neurology. Volume 19. New York, Raven Press, 1978, pp. 281-311.

- (29) LEE, P.N., GARFINKEL, L. Mortality and type of cigarette smoked. *Journal of Epidemiology and Community Health* 35(1): 16-22, March 1981.
- (30) MacKAY, A., NIAS, B.C. Strokes in young and middle-aged: Consequences to the family and to society. *Journal of the Royal College of Physicians of London* 13(2): 106-112, 1979.
- (31) McQUEEN, E.G. Hormonal steroid contraceptives: A further review of adverse reactions. *Current Therapeutics* 19: 176-200, October 1978.
- (32) MENOTTI, A., CONTI, S., GIAMPAOLI, S., MARIOTTI, S., SIGNORETTI, P. Coronary risk factors predicting coronary and other causes of death in fifteen years. *Acta Cardiologica* 35(2): 107-120, 1980.
- (33) NATIONAL CENTER FOR HEALTH STATISTICS. *Monthly Vital Statistics Report*. U.S. Department of Health and Human Services, Public Health Service, Office of Health Research, Statistics, and Technology, National Center for Health Statistics. DHHS Publication No. (PHS) 80-1120, Volume 29, No. 1, Supplement, April 28, 1980.
- (34) OKADA, H., HORIBE, H., OHNO, Y., HAYAKAWA, N., AOKI, N. A prospective study of cerebrovascular disease in Japanese rural communities, Akabane and Asahi. Part I: Evaluation of risk factors in the occurrence of cerebral hemorrhage and thrombosis. *Stroke* 7(6): 599-607, November-December 1976.
- (35) OSTFELD, A.M., SHEKELLE, R.B., KLAWANS, H.L. Transient ischemic attacks and risk of stroke in an elderly poor population. *Stroke* 4(6): 980-986, November-December 1973.
- (36) OSTFELD, A.M., SHEKELLE, R.B., KLAWANS, H., TUFO, H.M. Epidemiology of stroke in an elderly welfare population. *American Journal of Public Health* 64(5): 450-458, May 1974.
- (37) PAFFENBARGER, R.S., Jr., BRAND, R.J., SHOLTZ, R.I., JUNG, D.L. Energy expenditure, cigarette smoking, and blood pressure level as related to death from specific diseases. *American Journal of Epidemiology* 108(1): 12-18, July 1978.
- (38) PAFFENBARGER, R.S., Jr., WING, A.L. Chronic disease in former college students. XI. Early precursors of nonfatal stroke. *American Journal of Epidemiology* 94(6): 524-530, December 1971.
- (39) PETITTI, D.B., WINGERD, J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid hemorrhage. *Lancet* 2(8083): 234-236, July 29, 1978.
- (40) PETITTI, D.B., WINGERD, J., PELLEGRIN, F., RAMCHARAN, S. Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *Journal of the American Medical Association* 242(11): 1150-1154, September 14, 1979.
- (41) RHOADS, G.G., POPPER, J.S., KAGAN, A., YANO, K. Incidence of transient cerebral ischemic attack in Hawaii Japanese men. The Honolulu heart study. *Stroke* 11(1): 21-26, January-February 1980.
- (42) RINEHART, W., PIOTROW, P.T. Oral contraceptives—Update on usage, safety, and side effects. *Population Reports Series A*(5): 133-186, 1979.
- (43) ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Reports* 95(3): 213-222, May-June 1980.
- (44) ROYAL COLLEGE OF GENERAL PRACTITIONERS. Oral contraceptive study. Mortality among oral contraceptive users. *Lancet* 2(8041): 727-731, October 8, 1977.
- (45) ROYAL COLLEGE OF GENERAL PRACTITIONERS. *Oral Contraceptives and Health*. An interim report from the Oral Contraceptive Study of the Royal College of General Practitioners. Manchester, England, Pitman Publishing Corporation, 1974, 100 pp.

- (46) ROYAL COLLEGE OF GENERAL PRACTITIONERS. Oral contraceptive study. Further analysis of mortality in oral contraceptive users. *Lancet* 1(8219): 541-546, March 7, 1981.
- (47) SALONEN, J.T., PUSKA, P., TUOMILEHTO, J., HOMAN, K. Relation of blood pressure, serum lipids, and smoking to the risk of cerebral stroke: A longitudinal study in Eastern Finland. *Stroke* 13(3): 327-333, May-June 1982.
- (48) STADEL, B.V. Oral contraceptives and cardiovascular disease (First of two parts). *New England Journal of Medicine* 305(11): 612-618, September 10, 1981.
- (49) STADEL, B.V. Oral contraceptives and cardiovascular disease (Second of two parts). *New England Journal of Medicine* 305(12): 672-677, September 17, 1981.
- (50) STAMLER, J. What is happening with coronary heart disease in the United States? In: Hayase, S., Murao, S., MacArthur, C. (Editors). *Cardiology. Proceedings of the VIII World Congress of Cardiology, Tokyo, September 17-23, 1978.*
- (51) STEINMANN, B. Zur Pathogenese der Apoplexie im Alter unter 50 Jahren. [On the pathogenesis of apoplexy in persons below 50 years of age.] *Schweizerische Medizinische Wochenschrift* 99(31): 1098-1106, 1969.
- (52) TURNHEIM, M., HAVELEC, L., HEISS, W.-D., SUMMER, K. Eigenarten ischaemischer insulte bei jungen Ernachsensen. [Characteristic features of ischemic strokes in young adults]. *Weiner Klinische Wochenschrift* 89(4): 106-110, 1977.
- (53) VESSEY, M.P., DOLL, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. *British Medical Journal* 2(5599): 199-205, April 27, 1968.
- (54) VESSEY, M.P., DOLL, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. *British Medical Journal* 2(5658): 651-657, June 14, 1969.
- (55) WOLF, P.A., DAWBER, T.R., KANNEL, W.B. Heart disease as a precursor of stroke. In: Schoenberg, D.S. (Editor). *Neurological Epidemiology: Principles and Clinical Applications. Advances in Neurology.* Volume 19, New York, Raven Press, 1978, pp. 567-577.
- (56) WOLF, P.A., DAWBER, T.R., THOMAS, H.E., Jr., KANNEL, W.B. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. *Neurology* 28(10): 973-977, October 1978.